Product	Maltofer Fol Chewable tablets	
Country	Malaysia	
Manufacturer	COV	
SAP Number	3005248-05	**Min. Ver.:** 01
Manufacturer Identification Number	3005248/05	
Fonts	Helvetica (min. 9 pt)	
Dimensions	180 x 320 mm	

Colours/Flats
Black

Non-Printed Colours
Dye Cut

ID: 2311-070

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Maltofer® Fol

Chewable tablets

Pharmaceutical form: chewable tablets, chocolate flavour

Qualitative and quantitative composition
Each chewable tablet contains 100 mg of iron as iron(III)-hydroxide polymaltose complex (IPC) and 0.35 mg of folic acid

Excipients: microcrystalline cellulose, cocoa, sodium cyclamate, polyethylene glycol 6000, talc, vanillin, dextrates, chocolate essence.

Properties
Pharmacotherapeutical group: iron preparations, iron in combination with folic acid.

ATC Code: B03AD04

In iron(III)-hydroxide polymaltose complex, the polynuclear iron(III)-hydroxide core is superficially surrounded by a number of non-covalently bound polymaltose molecules resulting in an overall average molecular weight of approximately 50 kDa. The polynuclear core of IPC has a structure similar to that of the physiological iron storage protein, ferritin. IPC is a stable complex and does not release large amounts of iron under physiological conditions. Because of its size, the extent of diffusion of IPC through the membrane of the mucosa is about 40 times less than that of the hexaquo-iron(II) complex. Iron from IPC is taken up in the gut via an active mechanism.

Folic acid (folate) is a member of the Vitamin B group. It is a tetrahydrofolate precursor, a coenzyme involved in various metabolic processes including the biosynthesis of nucleic acid purines and thymidylates. Folic acid is required for nucleoprotein synthesis and maintenance of normal erythropoiesis

Therapeutic Indications
Treatment of iron deficiency without anaemia and iron deficiency anaemia, and prevention of iron and folic acid deficiency before, during and after pregnancy (during lactation).

Posology
Treatment of iron deficiency anaemia in pregnancy:
200 mg iron, 0.70 mg folic acid to 300 mg iron, 1.05 mg folic acid (2 to 3 tablets) daily until a normalisation of the haemoglobin (Hb) value is achieved. Afterwards, the therapy should be continued with 100 mg iron, 0.35 mg folic acid (1 tablet) daily at least until the end of the pregnancy to replenish the iron stores and to supplement the increased iron need during pregnancy.

Treatment of iron deficiency without anaemia and prevention of iron and folic acid deficiency:
100 mg iron, 0.35 mg folic acid (1 tablet) per day.

Paediatric population
The administration of Maltofer Fol chewable tablets has not been evaluated in children. Maltofer Fol chewable tablets are not suitable for children 12 years or younger.

Method of Administration
The daily dosage can be divided into separate doses or can be taken all at once. Maltofer® Fol chewable tablets can be chewed or swallowed whole and should be taken during or immediately after a meal.

Pharmacodynamic
The iron absorbed is bound to transferrin and is used for Hb synthesis in the bone marrow or stored primarily in the liver bound to ferritin.

Clinical Efficacy
During pregnancy, there is an increased requirement for iron which is approximately 0.8 mg/day in the first trimester and up to 6 mg/day during the third trimester of pregnancy. In addition, there is an increased requirement for folic acid, particularly during pregnancy. Low folic acid levels can lead to signs of deficiency in both mothers (anaemia, peripheral neuropathies) and the foetus (congenital neural tube defects).

Clinical studies have been carried out in pregnant women to investigate the safety and efficacy of the treatment of iron deficiency with or without anaemia, as well as to prevent an iron and folic acid deficiency with IPC treatment in combination with folic acid (Maltofer Fol). Changes in haematological parameters were compared during treatment with Maltofer Fol chewable tablets at a dose of 100 mg–300 mg iron/day in conjunction with 0.35 mg folic acid/day in comparison to iron(II) sulphate standard preparations with and without folic acid. A study investigated the efficacy of IPC with the addition of a folic acid supplement compared to intravenous iron administration, and another study examined the efficacy and tolerability of Maltofer Fol compared to a diet high in iron. In total, approximately 700 pregnant women with normal and decreased iron were included, and more than 400 of these patients received Maltofer Fol.

Treatment of pregnant women with Maltofer Fol showed similar improvements in haematological parameters compared to results with Maltofer in non-pregnant patients with at the same time a good tolerability. An improvement in the haemoglobin values to an average of 0.72 to 2.2 g/dL ($p<0.05$) as compared to the start of treatment was observed in the clinical studies following treatment with Maltofer Fol lasting between 30 days and 2.5 months. In addition, improvements were measured in serum ferritin (+5.74 mcg/L) and in red blood cell ferritin levels (on average +6.3 mcg/g or 5.74 mcg/g after treatment lasting 30 days or 2.5 months compared to the baseline).

An open study investigated the efficacy of Maltofer Fol (200 mg IPC/day for 10 days and 100 mg/day for 20 days) with supplemental vitamin B12 in pregnant women with iron deficiency anaemia. There was a significant increase in haemoglobin values as well as in the haematocrit, the number of erythrocytes and folic acid values. ($p<0.01$).

An open study with 43 young adults with varying degrees of iron deficiency anaemia between the ages of 14.5 and 17 years investigated the efficacy of Maltofer Fol on haemoglobin levels. The anaemia was corrected after 48 days of treatment in the group with mild anaemia. The Hb levels increased from 104.3 ± 1.7 g/L to 134.1 ± 1.3 g/L. In patients with moderate or severe anaemia, a significant increase in Hb level from 83.0 ± 0.4 to 116.4 ± 0.7 g/L for moderate and from 67.9 ± 0.9 g/L to 104.4±0.8 g/L for severe anaemia was achieved after 48–49 days of treatment. Correction of the anaemia was able to be achieved after 75–76 days of treatment in patients with moderate anaemia (Hb level = 133.2 ± 1.1 g/L) and after 82–83 days of treatment in patients with severe anaemia (Hb level = 134.4 ± 0.9 g/L).

Pharmacokinetic
Absorption
Studies with radio-labelled IPC show a good correlation between iron absorption and build-up of iron in haemoglobin. The relative absorption of iron correlates with the degree of iron deficiency (i.e. the greater the iron deficiency, the higher the iron absorption). In contrast to iron(II) salts, it was determined that food had no negative effect on the bioavailability of iron from Maltofer: significantly increased bioavailability of iron with concomitant ingestion of food was demonstrated in a clinical study, while three other studies showed a positive trend but no clinically significant effects. Around 80% of folic acid is absorbed in the small intestine, with maximum absorption occurring after 30–60 minutes.

Elimination
Iron that is not absorbed is eliminated in the faeces. Folic acid is mainly excreted in the urine.

Preclinical data
Non-clinical data obtained for IPC does not reveal any special hazards for humans based on conventional studies of individual dose toxicity and repeated dose toxicity, genotoxicity or reproduction and development toxicity.

The LD50 of IPC, which was determined in animal trials with mice and rats, was higher than an orally administered dose of 2,000 mg of iron per kg of body weight.

Contraindications
- Known hypersensitivity or intolerance to iron(III)-hydroxide polymaltose complex, folic acid or any of the excipients.
- Iron overload (e. g. haemochromatosis, haemosiderosis)
- Disturbances in iron utilisation (e. g. lead anaemia, sideroachrestic anaemia, thalassaemia)
- Anaemia not caused by iron deficiency (e. g. haemolytic anaemia or megaloblastic anaemia due to vitamin B12 deficiency).

Special warnings and special precautions for use
Anaemias should always be treated under the supervision of a doctor. If therapeutic success (increase in haemoglobin by about 2–3 g/dL after 3 weeks) is not achieved, treatment should be reconsidered. Maltofer Fol contains folic acid so it may mask deficiencies of vitamin B12. A potential vitamin B12 deficiency must be ruled out before the start of treatment in anaemic patients due to the risk of irreversible neurological dysfunctions, see «Contraindications».

This medicine contains 10 mg sodium (main component of cooking/table salt) in each tablet. This is equivalent to 0.5% of the recommended maximum daily dietary intake of sodium of 2 g for an adult.

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Infections or tumours may cause anaemia. Since iron can be utilised only after correcting the primary disease, a benefit/risk evaluation is advisable.

During treatment with Maltofer® Fol, there may be dark discolouration of the faeces (stools); however this is of no clinical relevance.

Interactions with other medicaments and other forms of interaction
Interactions of IPC with tetracycline or aluminium hydroxide were investigated in 3 human studies (crossover design, 22 patients per study). No significant reduction in the absorption of tetracycline was observed. The plasma tetracycline concentration did not fall below the level necessary for efficacy. Iron absorption from IPC was not reduced by aluminium hydroxide or tetracycline. Iron(III) hydroxide polymaltose complex can therefore be administered at the same time as tetracycline or other phenolic compounds, as well as aluminium hydroxide.

Studies in rats with tetracycline, aluminium hydroxide, acetylsalicylate, sulphasalazine, calcium carbonate, calcium acetate and calcium phosphate in combination with vitamin D3, bromazepam, magnesium aspartate, D-penicillamine, methyldopa, paracetamol and auranofin have not shown any interactions with IPC.

Similarly, no interactions with food constituents such as phytic acid, oxalic acid, tannin, sodium alginate, choline and choline salts, vitamin A, vitamin D3 and vitamin E, soya oil and soya flour were observed in in vitro studies with IPC. These results suggest that IPC can be taken during or immediately after food intake.

The haemoccult test (selective for Hb) for the detection of occult blood is not impaired and therefore there is no need to interrupt iron therapy.

Concomitant administration of parenteral and oral iron is not recommended since the absorption of oral iron would be inhibited.

Folic acid therapy may increase phenytoin metabolism, resulting in decreased phenytoin serum concentrations, particularly in folate deficient patients. Although this interaction is not usually clinically important, an increase in seizure frequency may occur in some patients. Anyone taking phenytoin or other anti-convulsant medications should consult with a medical doctor before taking a folic acid supplement.

It has been reported that the concurrent administration of chloramphenicol and folic acid in folate- deficient patients may result in antagonism of the haematopoietic response to folic acid. Although the importance and mechanism of the interaction is unclear, the haematologic response to folic acid in patients receiving both drugs should be carefully monitored.

Pregnancy and lactation

Pregnancy
Clinical data of exposed pregnancies exhibited no undesirable effects on pregnancy or on the health of the foetus or newborn infant. Data from epidemiological studies is not available. Animal studies did not show any reproductive toxicity (see Preclinical Data). Caution is advised for use during pregnancy. As a precautionary measure, Maltofer should only be taken after consulting a doctor.

Breast-feeding
It is not known whether iron from the iron (III)-hydroxide polymaltose complex is excreted in human milk. Human milk naturally contains iron bound to lactoferrin. As a precautionary measure, Maltofer Fol should only be taken should only be taken during breast-feeding after consulting a doctor.

Effects on ability to drive and use machines
No relevant studies have been performed. However, it is unlikely that Maltofer Fol has any effect on the ability to drive and use machines.

Undesirable effects
The safety and tolerability of Maltofer Fol® were assessed in a meta-analysis of 24 publications or clinical trial reports with a total number of 1473 exposed patients. The most significant adverse drug reactions reported by these trials occurred in 4 system organ classes (see below).

Discoloured faeces are a well known adverse drug reaction of oral iron preparations but it is not considered clinically relevant and is often not reported. Other commonly observed undesirable effects were gastrointestinal disorders (nausea, constipation, diarrhoea and abdominal pain).

System Organ Class	Very common (≥1/10)	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (<1/1,000)
Gastrointestinal Disorders	Discoloured faeces*	Diarrhoea, nausea, abdominal pain (including: abdominal pain, dyspepsia, epigastric discomfort, abdominal distension), constipation	Vomiting (including: vomiting, regurgitation), teeth discolouration, gastritis.	
Skin and Subcutaneous Tissue Disorders			Pruritus, rash (including: rash, macular rash, rash vesicular)**, urticaria**, erythema**.	
Nervous System Disorders			Headache	
Musculoskeletal, connective and bone disorders				Muscle spasms (including: involuntary muscle contraction, tremor), myalgia.

* Discoloured faeces were reported in the meta-analysis at a lower frequency but they are generally a well known adverse drug effect of an oral iron therapy. For this reason, Discoloured faeces was classified under very common undesirable effects.
** Events came from spontaneous reports after market introduction, with an estimated incidence of <1/491 patients (upper limit of 95% confidence interval).

Overdose
In cases of overdose, iron accumulation or intoxication is unlikely with Maltofer® Fol due to the low toxicity of iron(III)-hydroxide polymaltose complex (i.e., in mice or rats: lethal dose, 50% (LD50) > 2,000 mg Fe/kg body weight) and controlled uptake of iron. No cases of accidental poisoning with fatal outcome have been reported. There are reports that an excessive dose of folic acid may cause changes to the central nervous system (namely changes in mental state, changes to the sleep pattern, irritability and hyperactivity), nausea, abdominal distension and flatulence.

Storage
Keep all medicines out of reach of children. Below 30 °C in the original container.
Keep in the original package (i.e. outer carton) in order to protect from light.

Presentation
3 aluminium blisters, each blister contains 10 chewable tablets
Manufactured by Corden Pharma Fribourg SA (Switzerland) for Vifor (International) Inc. (Switzerland)

Product Registration Holder
Zuellig Pharma Sdn Bhd No.15 Persiaran Pasak Bumi, Seksyen U8,
Perindustrian Bukit Jelutong,
40150 Shah Alam,
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Date of Revision: August 2023

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